LISTING OF THE CLAIMS AS AMENDED

Please amend claims 17-18, 27-28, and 31 so that they read as-follows:

Claims 1-16 (cancelled)

17. (Currently Amended) A biological tissue comprising endothelial cells which may be induced to generate a compound which down-regulates the surface expression of a cell adhesion molecule by the cells, the compound being ~~either (a) a polynucleotide complementary in sequence to part of the gene or mRNA that encodes the cell adhesion molecule, (b) a polynucleotide comprising a ribozyme sequence that specifically targets a gene or mRNA that encodes the cell adhesion molecule, or (c)~~ a peptide or polypeptide with specific binding affinity for the cell adhesion molecule, the endothelial cells comprising a vector which encodes the peptide or polypeptide under the control of an inducible promoter.

18. (Currently Amended) A tissue according to claim ~~20~~ 17, wherein said polypeptide ~~(c)~~ is a bispecific fusion protein.

19. (Withdrawn) A polypeptide comprising a binding region capable of binding to a cell adhesion molecule and a signalling region for subcellular targeting of the polypeptide such that is not transported to the cell surface.

20. (Withdrawn) A polypeptide according to claim 22, which comprises an antibody or antibody fragment.

21. (Withdrawn) A polypeptide according to claim 23, which comprises a single chain Fv fragment.

22. (Withdrawn) A polypeptide according to claim 22, wherein the signalling region for subcellular targeting of the polypeptide comprises a localisation signal for the endoplasmic reticulum.

23. (Withdrawn) A polypeptide according to claim 25, wherein the signalling region comprises the amino acid sequence KDEL at the C terminus of the polypeptide.

24. (Withdrawn) A polypeptide according to claim 22, wherein said binding region has affinity for any one of the adhesion molecules VCAM-1, ICAM-1, LFA-1, CD2, PECAM, CD31, IAP, CD47 or integrin $\alpha v\beta 3$.

25. (Withdrawn) A polynucleotide encoding a polypeptide according to claim 22.

26. (Withdrawn) A vector comprising a polynucleotide according to claim 28.

27. (Currently Amended) An endothelial cell ~~comprising a~~ transformed with a nucleic acid that encodes a polypeptide, ~~polynucleotide according to claim 28 or a vector according to claim 29~~ wherein said polypeptide comprises a binding region capable of binding to a cell adhesion molecule and a signalling region for subcellular targeting of the polypeptide such that the cell adhesion molecule is not transported to the cell surface.

28. (Currently Amended) A biological tissue comprising a cell according to claim ~~30~~ 27.

29. (Withdrawn) A non-human animal comprising biological tissue according to claim 31 and/or a cell according to claim 30.

30. (Withdrawn) An animal according to claim 32, wherein said animal is a transgenic pig or sheep.

31. (Currently Amended) A method of ~~rendering a~~ prolonging survival of a tissue or organ graft ~~suitable for transplantation~~, comprising expressing a polypeptide ~~according to claim 22~~ in endothelial cells in said tissue or organ~~, thereby down-regulating the~~ so that surface expression of a cell adhesion molecule is down regulated,

wherein said polypeptide comprises a binding region capable of binding to a cell adhesion molecule and a signaling region for subcellular targeting of the polypeptide such that the cell adhesion molecule is not transported to the cell surface, and

wherein down regulation of the surface expression of said cell adhesion molecule prolongs the survival of a tissue or organ graft.

32. (Withdrawn) A method of transplantation, comprising transplanting biological tissue according to claim 31 from a donor animal into a recipient animal.

* * * * *

REMARKS

Claims 17-32 are currently pending in this application. Claims 19-26, 29, 30 and 32 have been withdrawn from consideration as directed to non-elected subject matter. Claims 17, 18, 27, 28 and 31 are under consideration and have been amended, *supra*, without prejudice or admission.

Pending dependent claims 18 and 28 have been amended pursuant to the Examiner's request, so that they reflect the Examiner's change of the claim numbering under 37 CFR § 1.126. Independent claim 17 has also been amended pursuant to the Examiner's request, so that it only reads on the elected subject matter of this invention. Specifically, amended claim 17 is now restricted to tissue comprising endothelial cells that express a polypeptide which down-regulates expression of a cell adhesion molecule or "CAM". In addition, claim 17 has been amended to specify that endothelial cells in the claimed tissue comprise a vector construct that encodes the peptide or polypeptide under the control of an inducible promoter. As support for these amendments, the Examiner's attention is invited, *e.g.*, to page 9, lines 16-26 and to Example 3 (beginning on the last line of page 15 and continuing to page 17, line 13) in the application as-filed. Also, claim 17 as amended now particularly specifies that it is the *surface* expression of a cell adhesion molecule that is down-regulated by the polypeptide. This limitation is supported, *e.g.*, on page 5 at lines 15-18 of the application as filed.

Claims 27 and 31 have been amended to incorporate the limitations of withdrawn claim 19 and, again, to specify that it is the *surface* expression of a cell adhesion molecule that is down-regulated. Claim 31 has additionally been amended to particularly specify that the claimed method prolongs the survival of a tissue or organ graft. Amended claim 31 also particular specifies that this goal is accomplished by down-regulating the surface expression of a cell adhesion molecule.

The specification has also been amended to incorporate the sequence identity numbers (SEQ ID NOS) in the accompanying Substitute Sequence Listing, and to incorporate the Abstract of the Disclosure attached hereto as Exhibit Tab A. Applicants respectfully point out that this application is a 371 of PCT/GB99/03888. The attached Abstract is identical to the Abstract that was

originally filed and published as part of that PCT application. Hence, the Abstract does not contain new matter.

As explained above, none of the amendments, presented here introduce new matter to this application. Entry and consideration of these amendments are therefore respectfully requested.

I. Miscellaneous Claim Objections

Claims 17, 27, 28, and 31 stand objected to due to various informalities. Claims 17 has been amended so that it only reads on the elected subject matter of this application. Dependent claims 18 and 28 have been amended to reflect the Examiner's renumbering under under 37 CFR § 1.126. Claims 27, 28 and 31 have also been amended so that they no longer depend from non-elected claims. Finally, claim 28 has been amended to include an article at the beginning of the claim. Accordingly, it is believed that each of the Examiner's objections to the pending claims has now been obviated.

II. Miscellaneous Objections to the Specification

The Examiner has also objected to various informalities to the specification as filed. In particular, the Examiner has noted that this application contains biological sequences without appropriate sequence identification numbers (SEQ ID NOS). The Office Action also alleges that the application does not contain an Abstract of the Disclosure.

The specification has been amended to identify, where appropriate, SEQ ID NOS for the biological sequences. Applicants are also submitting herewith both a paper copy and a computer readable form (CRF) of a Sequence Listing for this application. A Sequence Listing Transmittal also accompanies these submissions, verifying that the content of the paper and CRF copies of the Sequence Listing are identical and that they do not contain new matter.

An Abstract of the Disclosure is also submitted here, at Exhibit Tab A, for entry into the specification as part of the amendments, *supra*. As noted above, this Abstract is identical to the one that was originally filed and published for this PCT application. Accordingly, the Abstract submitted here does not contain new matter.

For all of the above reasons, Applicants believe that the objections to the specification have now been obviated and should be withdrawn.

III. The Rejections Under 35 U.S.C. § 101 Should be Withdrawn

Claims 17 and 18 stand rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. In particular, the Office Action alleges that claim 17 reads on a product of nature. In response, claim 17 has been amended to specify that the endothelial cells in a tissue sample of the invention comprise a signature vector. Such cells do not exist in nature and consequently, a tissue sample containing such cells is *not* a product of nature. Applicant therefore respectfully submit that the rejection under 35 USC § 101 should be withdrawn.

IV. The Rejection Under 35 U.S.C. § 112, first paragraph, Should Be Withdrawn

Claims 17, 18, 27, 28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The Examiner states that claim 17 is not enabled because "[w]hile it is true that the surface expression of VCAM is down regulated, the overall expression is not down regulated" (*See*, the Office Action in the first full paragraph at page 8). The Office Action presents a similar argument for claim 31 (*See*, page 13 of the Office Action in the second full paragraph) In response, Applicants point out that Claims 17 and 31 have been amended to recite "a compound which down-regulates the *surface* expression of a cell adhesion molecule". Applicants therefore respectfully request that this rejection be withdrawn.

The Examiner also states that claim 17 is not enabled because "the specification fails to teach how the adhesion molecules are down regulated when the endothelial cells are transfected with a non-bispecific polypeptide as recited in claim 17." *Id.* Initially, Applicants note that claim 17 requires that the endothelial cells *generate* a peptide or polypeptide with specific binding affinity for the cell adhesion molecule. The endothelial cells are not transfected with the peptide or polypeptide.

Rather the cells are transfected with a vector which encodes the polypeptide under the control of an inducible promoter. Claim 17 has been amended to particularly recite that the endothelial cells comprise "a vector which encodes the peptide or polypeptide under the control of an inducible promoter".

As set forth on page 8 of the specification, the peptide or polypeptide encoded may have "binding affinity and specificity against two or more different epitopes on a cell adhesion molecule such as VCAM", i.e., a bispecific fusion protein. Although one skilled in the art will realize that such a bispecific fusion protein would improve efficiency of the knockout of the cell adhesion molecule, expression of the cell adhesion molecule can be down-regulated by a protein having affinity and specificity against only one region of the cell adhesion molecule. Applicants respectfully request that this enablement rejection be withdrawn.

Beginning on the first full paragraph on page 9 of the Office Action, the Examiner begins a lengthy discussion regarding the "sole utility of the claimed tissue is a pharmaceutical composition suitable for xenotransplantation", and states that "in light of the state of the art, the specification fails to support the full scope of the claims." The Examiner then proceeds to discuss various problems barriers to transplantations "as of post-filing dates", apparently suggesting that Applicants have not overcome all problems relevant to xenotransplantation.

Applicants respectfully note that all questions of enablement are evaluated against the claimed subject matter, not against all possible problems relevant to the field in which the invention relates. See M.P.E.P. § 2164.01 (noting requirements to determine whether *a particular claim* is supported by the disclosure). Claim 31 has been amended to more particularly specify a method that prolongs survival of a tissue or organ graft. Hence, Applicants do not claim a panacea that solves all the problems of xenotransplantation, and neither should that be expected of the Applicants. Instead,

the invention provides improvements to the xenotransplantation methods known as of the priority date, and this substantial contribution to the art should be recognized.[1]

The claimed subject matter relates to biological tissue or organs comprising endothelial cells in which the surface expression of cell adhesion molecules is down-regulated by a peptide or polypeptide with specific binding affinity for the cell adhesion molecule. The Examiner admits that "the specification teaches transducing endothelial cells with a vector comprising an inducible promoter" (Office Action dated March 18, 2003, page 15, first full paragraph). The Examiner alleged, however, that "the specification fails to teach how to deliver the nucleic acid . . . where the endothelial cells are embedded in a solid organ" (Office Action dated March 18, 2003, page 11, first full paragraph). Pages 9-12 of the specification provide various examples of vectors and delivery systems that are available to the person of ordinary skill depending on the particular application, along with various cited references for further consultation. More specifically, lines 15-30 on page 11 of the specification discuss methods for delivering gene therapy to tissues in such applications.

The Examiner also states that "the *in vivo* efficiency of the polypeptide in reducing surface expression of adhesion molecules and thus the efficacy in suppression of xenotransplant rejection" is not taught. Applicants submit that sufficient data has been set forth in the specification (see Example 6, Figures 9A and 9B) to reasonably establish that the reduced binding of the leukocytes to the endothelial cell monolayer observed *in vitro* would be reproduced *in vivo*. The Manual of Patent Examining Procedure (MPEP) states the following regarding the value of *in vitro* data in establishing a therapeutic utility (MPEP 2107.03 (III)):

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays . . . almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

[1] As an aside, the problems presented by the Examiner are not necessarily indicative of problems that would present themselves in the practice of the present invention. For example, the Examiner relies upon Dorling (*Transplantation* 1996, 62:1127-1136). As explained below, however, Dorling does not describe the specific inhibition of a cell adhesion molecule, but is actually concerned with the "accommodation response" in transplanted endothelial cells exposed to normal levels of circulating antigraft antibodies. *See* Dorling in lines 1-3 of the Abstract.

Since reduced cell adhesion has been firmly established *in vitro*, Applicants submit that the therapeutic effect of the activity in rendering tissues less likely to be rejected, and thus more suitable for transplantation, has also been established. Applicants request withdrawal of the claims rejections on these grounds.

For all of the above reasons, Applicants respectfully submit that the rejections for enablement under 35 U.S.C. § 112 have been obviated. Applicants therefore respectfully request that these rejections be withdrawn.

V. Rejections based on 35 U.S.C. § 112, second paragraph, Should be Withdrawn

Claims 17, 18 and 31 have been rejected under the second paragraph of 35 USC § 112 as being indefinite. At the outset, Applicant note that although the Office Action does state that claim 18 is rejected as indefinite, no explanation is offered explaining why that claim fails to particularly point out and distinctly claim elected subject of this application. Indeed, Applicants believe that claim 18 is completely definite with the meaning of 35 USC § 112, second paragraph. It is therefore assumed that the claim has been rejected in error.

Claim 17 is allegedly "vague and indefinite" apparently because the means of inducing an endothelial cell to generate a polypeptide with specific binding affinity for a cell adhesion molecule" are unclear. Claim 17 has been amended to recite that the cell comprises "a vector which encodes the peptide or polypeptide under the control of an inducible promoter". Withdrawal of this rejection is respectfully requested.

Claim 31 is rejected as "vague and indefinite" because it is allegedly incomplete. The Examiner states that it is unclear how the goal of the claimed method is achieved. Claim 31 has been amended to more particularly specify that down regulating the surface expression of the cell adhesion molecule prolongs the survival of a tissue or organ graft. Hence, the amended claim clearly states how the goal of that method is accomplished.

For all of the above reasons, Applicant respectfully submit that the claim rejections under the second paragraph of 35 USC § 112 should be withdrawn.

VI. Rejections based on 35 U.S.C. § 102 Should be Withdrawn

Claim 17 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Klein *et al.*, *Eur. J. Cell Bio.* 1997, 72(S43):101.("Klein"). The Examiner alleges that Klein *et al.* teach different cell endothelial cell lines which may be induced to generate a polypeptide that down regulates a cell adhesion molecule. Applicants respectfully disagree, and submit that, at most, the Klein reference only teaches that the surface expression of a cell adhesion molecule (CAM) in endothelial cells may be reduced by exposing the cells to hypoxic or hyperoxic conditions. No mention is made of inducing anti-CAM peptides that can down-regulate the surface expression of cell adhesion molecules. Thus the limitation "a peptide or polypeptide with specific binding affinity for the cell adhesion molecule" is neither taught nor suggested.

Claim 17 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Orosz *et al.*, *Transplant* 1993, 56:453-60 ("Orosz"). The Examiner alleges that Orosz teaches a cardiac tissue comprising endothelial cells, which may be induced to generate a polypeptide that down regulates a cell adhesion molecule. Applicants submit that Orosz merely teaches the intraperitoneal injection of an anti-CAM antibody leads to increased graft survival. There is no disclosure of *in situ* expression of such antibodies by the host. Thus the limitation "endothelial cells which may be induced to generate a compound which down-regulates the surface expression of a cell adhesion molecule" is not taught or suggested by Orosz.

Claims 27 and 28 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Greenman *et al.*, *J. Immunol. Methods* 1996, 194:169-180 ("Greenman"). Claim 27 has been amended to recite "an *endothelial* cell transformed with a nucleic acid that encodes a polypeptide". Claim 28 comprises "a cell according to claim 27" and further recites "biological tissue". Biological tissue is defined in the specification as being "any tissue suitable for transplantation to a mammal" (page 5, line 5), which excludes CHO (chinese hampster ovary) cells. The Examiner has acknowledged, however, that "Greenman *et al.* do not express [a] polypeptide in endothelial cells" (*see* the Office Action at page 19, line 2). None of these limitations is taught or suggested by Greenman *et al.* and, hence, the Greenman reference cannot anticipate pending claims 27 and 28.

Claims 27 and 28 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Yuan *et al.*, *Biochem. J.* 1996, 318:591-596 ("Yuan"). The Examiner alleges that "Yuan et al. teach RD and Jurkat cells (collection of cells) transduced with a polynucleotide encoding a fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for VLA-4 (a cell adhesion molecule)." Contrary to the Examiner's assertion, however, VLA-4 is not a cell adhesion molecule, but rather a counter-ligand for a cell adhesion molecule (VCAM-1) (see page 3, lines 7-11 of the Specification). Claims 27 recites a peptide comprising "a binding region capable of binding to a cell adhesion molecule", and claim 28 depends from claim 27. This limitation is not taught or suggested by Yuan et al.

Furthermore, the Examiner notes that "Yuan *et al.* do not express the polypeptide in endothelial cells." Claims 27 has been amended to recite "an endothelial cell comprising a peptide or polypeptide according to claim 17". Claim 28 recites a biological tissue comprising a cell according to claim 27. These limitations are also not taught or suggested by Yuan.

VII. Rejections under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 17, 18 and 31 have been rejected under 35 U.S.C. § 103(a) as being obvious, and therefore unpatentable, over the combined teachings of Greenman *et al. J. Immunol.* Methods 1996, 194:169-180 ("Greenman") and Klein *et al.*, *Eur. J. Cell Bio.* 1997, 72(S43):101 ("Klein"). In addition, these claims have also been rejected as being obvious over the combined teachings of Yuan *et al.*, *Biochem J.* 1996, 318:591-596 ("Yuan") in view of Dorling *et al.*, *Transplantation* 1996, 62:1127-1136 ("Dorling"). Each of these prior art rejections is discussed in turn, below.

A. *The legal standard for obviousness*

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a

reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach *all* of the claimed limitations. See, M.P.E.P. § 2143.

The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See *Id.*, *citing In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Obviousness can only be established by combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. M.P.E.P. § 2143.01; *See, also, In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990).

B. *Greenman in view of Klein*

According to the Office Action, Greenman describes a method for inhibiting CD2 expression in CHO (chinese hamster ovary) cells using an intracellular antibody fragment. The Examiner further alleges that Greenman teaches that "the general approach of intracellular single chain antibody expression provides a simple, efficient way of studying the function of molecules that cannot be studied by current techniques" (*see*, the Office Action at page 18).

In fact, however, Greenman teaches that the inhibition of CD2 using this method was not complete. (*See* Greenman, line 8 of Abstract; and in col. 1, lines 3-7 on page 178). Greenman concludes that "using [single chain antibody fragments] to block protein expression specifically . . . is clearly not straightforward" (Greenman in col. 1, lines 45-47 on page 179).

Klein is merely an abstract describing experiments where endothelial cells were exposed to different oxygen tensions (e.g., normoxic, hypoxic and hyperoxic conditions). Klein reports the effects of such conditions on the expression of certain cell adhesion molecules ("CAMs") by the endothelial cells, including ICAM-1, VCAM-1, and E-selectin. However, Klein does not inhibit the expression of those CAMs. Nor does he ever suggest that it might be desirable to do so. Instead,

Klein merely states that CAMs are "involved in intercellular activities of the relevant cell types" and that his "[endothelial cell] culture models may give us much deeper understanding of processes at the vessel wall". Klein does not explain what these processes are or how they might be mediated by the CAMs. Certainly, there is nothing in Klein's teaching to indicate that the cell adhesion molecules might be involved in xenograft rejection, or that by inhibiting a cell adhesion molecule it could be possible to render a tissue or organ more suitable for such transplantation.

Greenman overcome any of the above-describe deficiencies in Klein. Although Greenman may describe a general method for inhibiting the expression of certain cell surface molecules, Greenman does not teach or suggest any desirability for inhibiting the expression of particular cell surface molecules of that CD2. In particular, Greenman does not teach or suggest any desirability for inhibiting the expression of a CAM. Nor does Greenman teach or suggest that the techniques described in his publication might be successfully applied to other cell types, such as endothelial cells.

Even if the skilled artisan were somehow motivated to combine these references, the teachings of Greenman would not provide any reasonable expectation of success. As stated above, Greenman teaches that the inhibition of the cell adhesion molecule on CHO cells was "incomplete" and "clearly not straightforward". Hence, a person of ordinary skill could not reasonably expect success when applying these methods to epithelial cells, especially considering that epithelial cells were not considered in Greenman.

Both the motivation to combine references and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See M.P.E.P. § 2142, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990). As explained above, neither Greenman nor Klein provides any motivation for inhibiting CAM expression on the surface of endothelial cells. Nor do the references provide any reasonable expectation of success. Applicants therefore respectfully submit that the rejection for obviousness over Greenman in view of Klein should be withdrawn.

C. *Yuan in view of Dorling*

Claims 17, 18, and 31 also stand rejected as being obvious over Yuan *et al.* in view of Dorling *et al.*

Yuan is said to describe a method a method for inhibiting VLA-4 expression in Jurkat cells, a cell line derived from human T-cell leukemia cells. Specifically, Yuan inhibits VLA-4 expression in those cells using intracellular single chain antibodies.

Dorling describes experiments in which immortalized porcine endothelial cells were exposed to *extracellular* polyclonal human antibodies. However, those antibodies were not expressed in the endothelial cells and are not specific for VCAM or any other cell adhesion molecule. Rather, the extracellular antibodies administered by Dorling simulated exposure of transplanted endothelial cells to human antibodies after xenotransplantation. Dorling reports that the exposure of those porcine cells to polyclonal human antibodies induced a resistance to cell lysis upon exposure to other human antibodies specific for a gal α (1-3) gal epitope that is expressed on the porcine cells. Dorling also reports that a down regulation of VCAM in the porcine cells accompanies the cells' resistance to lysis. However, Dorling does not teach or suggest the specific intracellular inhibition of VCAM or any other cell adhesion molecule. The downregulation of VCAM that Dorling observes is instead characterized as part of the endothelial cells' "accomodation response" when exposed to normal levels of circulating graft antibodies.

Yuan also does not teach or suggest modifying the expression of a cell adhesion molecule in endothelial cells. Contrary to what is stated in the Office Action, VLA-4 is not a cell adhesion molecule. Rather, VLA-4 is a counter-ligand for the cell adhesion molecule VCAM-1 (see, in particular, the specification at page 3, lines 7-11). Moreover, Yuan merely inhibits the expression of VLA-4 in Jurkat cells "as a novel means for modulating integrin expression" (Yuan in the last paragraph of the right-hand column on page 595). Nothing in Yuan suggests that it might be desirable to similarly inhibit the expression of other molecules (*e.g.*,cell adhesion molecules) on the surface of endothelial or any other cell type.

For all of the above reasons, Applicants respectfully submit that the present Office Action fails to establish a *prima facie* case for obviousness and that these rejections should be withdrawn.

VIII. Conclusion

Applicants respectfully request entry of the foregoing amendments and remarks in the prosecution history of this application. The claims as amended are believed to be in better condition for allowance. Allowance of all of the claims is earnestly solicited.

Respectfully submitted,

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Abstract

The invention relates to the suppression of graft rejection, particularly to the suppression of xenograft rejection. In particular, the invention relates to biological tissues that contain endothelial cells that may be induced to generate a compound which down-regulates the expression of a cell adhesion molecule in these cells.